

A "Second Generation" Stilbestrol Alert

A Memo to Physicians of California
from the
CMA Committee on
Pharmacy and Therapeutics

DURING THE LATE 1940's and early 1950's many physicians administered diethylstilbestrol to high-risk pregnant patients. Now the medical profession throughout the country is confronted with an association between maternal ingestion of this medication and the appearance of vaginal adenocarcinoma in female offspring years later.

This note is a reminder to physicians to consider paying particular attention to the offspring of diethylstilbestrol-treated patients to check for vaginal cancer, at least yearly. In addition, physicians should watch for and investigate promptly cases of irregular vaginal bleeding or other symptoms that can be due to an early malignant lesion, particularly in the young female population.

If any such cases are found, they should be treated promptly, and a report* of such cases should be made voluntarily to the State Department of Public Health, which is collaborating with the National Registry in Boston.†

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CLINICAL CARDIOLOGY SERIES

Treatment of Cardiogenic Shock

Part II

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Material Supplied by the American Heart Association

Assisted Circulation

AS INDICATED IN PART I of this review, the major abnormality in cardiogenic shock is failure of the left ventricle as an effective pump. Therefore considerable effort has been expended in the development of cardiac assist devices to help the left ventricle which has been damaged as a consequence of a myocardial infarction.

Many lessons concerning prolonged assisted circulation were learned from surgical procedures utilizing extracorporeal circulation. Although the heart-lung machine may take over completely the functions of oxygenation and pumping of blood, there are many limitations to this technique for patients in cardiogenic shock. The need for thoracotomy in a critically ill patient virtually rules out any potential efficacy of this approach. In addition, the problems of hemolysis, plasma protein changes, clotting, infection and post-perfusion lung make prolonged extracorporeal circulatory techniques unfeasible for patients with cardiogenic shock.

Modifications of total extracorporeal circulatory assist have been utilized as temporary measures to help support a failing circulation. Veno-arterial pumping is one of these modifications. With this method, blood is withdrawn through a cannula introduced into the central venous system from the femoral vein. Blood is pumped into the arterial system from the femoral vein. If the venous blood is passed through an oxygenator the patient is on

Part II of a two-part article. Part I appeared in the January issue.

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partial heart lung bypass for all practical purposes. If an oxygenator is not used, the procedure is much simpler but anticoagulant drugs still are necessary to prevent clotting within the system. It has been demonstrated that the lower body and extremities can tolerate prolonged periods of perfusion with venous blood.

Left Heart Bypass

This method of assisted circulation removes oxygenated blood from the left atrium and returns it to the systemic circulation. Flow to the left ventricle is thereby diminished by the amount removed from the left atrium. The pump is in series with the right ventricle and lungs but in parallel with the left ventricle. By reducing cardiac inflow the distended left ventricle is given some degree of rest. It is likely that myocardial oxygen consumption is diminished as end diastolic ventricular volume and radius are decreased. Left heart bypass may be accomplished with or without thoracotomy. In the context of a patient in cardiogenic shock, a method requiring thoracotomy is obviously not feasible. As an adjunct to post-operative care this method has been utilized with some success.

A method of left heart bypass which does not require thoracotomy has been developed. A trans-septal cannula introduced into the external jugular vein is passed across the atrial septum into the left atrium. Although this method of cardiac assist was reported more than ten years ago, there is still no clinical trial demonstrating its efficacy for patients after a myocardial infarction.

Although any of the above mentioned forms of assisted circulation do reduce the flow work of the left ventricle, it has been demonstrated that myocardial oxygen consumption is much more closely related to pressure work. A method of assisted circulation that reduced the pressure work of the left ventricle would theoretically be of considerable benefit in reducing myocardial oxygen requirements.

Arterio-arterial pumping or counterpulsation is a form of assisted circulation that can reduce the systolic pressure against which the left ventricle must pump. In addition counterpulsation raises aortic diastolic pressure thereby increasing coronary bloodflow. In 1961 Harken et al reported on a counterpulsation device which involved cannulation of the femoral arteries. By synchronization with the electrocardiogram the pump aspirated blood from the femoral arteries during cardiac

systole and returned blood to the central circulation during cardiac diastole. Considerable diastolic augmentation was achieved. Other investigators, using synchronized counterpulsation in dogs, found that myocardial oxygen consumption decreased by more than 20 percent and coronary bloodflow was increased by 50 percent.

A variation upon the method of counterpulsation is that produced by the use of an intra-aortic balloon. This technique involves the inflation of an intra-aortic balloon at the onset of diastole and its deflation at the onset of systole. The advantages of this method are that it is totally intravascular and no blood is handled outside the body. There is less hemolysis in this technique than in counterpulsation devices which depend upon aspiration and return of blood to the vascular system for their hemodynamic effects. Heparin must be used, however, because of clotting of blood around the balloon. Rupture of the balloon with introduction of gas emboli into the vascular system is a potential hazard. Damage to the aortic wall by overdistention of the balloon may occur. Although an arteriotomy must be made for introduction of the balloon into the vascular system, there is no need for the diversion of blood through a conduit of foreign material.

Because of the desirability of having a cardiac assist device which is completely non-invasive, counterpulsation utilizing external body compression has been a goal of several groups of investigators. Such a device could be applied quickly, be free of any extracorporeal handling of blood, have no need for anticoagulants and would not involve any operative intervention. Because of these features it might be available to a patient earlier in the course of cardiogenic shock before prolonged hypofusion of vital organs made survival unlikely. Counterpulsation of the extremities involves displacement of blood retrograde into the central aorta during diastole and increasing the capacity of the arterial system during systole so as to draw blood from the aorta.

Dennis and his associates utilized a pressure sleeve on the hindlimbs of dogs and applied synchronous counterpulsation. Osborn utilized a half-body pressure suit but this was found to be uncomfortable when applied to normal volunteers. Keith found similar results when human volunteers were utilized. Soroff and his associates have also evaluated external pressure suits with and without simultaneous external cardiac massage. The combination of external assist plus external

cardiac massage was more successful in resuscitating dogs that were in ventricular fibrillation than was external assist alone.

In 1968 a series of physiologic studies leading to the development of an external cardiac assist device called "the sequenced pulsator" was initiated by the author and several of his colleagues. The rationale of sequenced pulsation in contrast to nonsequenced external pulsation is based on theoretical considerations underlying the effect of externally applied pressure to varying sized vessels in the extremity. Large vessels with a low ratio of wall thickness to lumen collapse more readily in response to externally applied pressure than do smaller vessels which have a high ratio of wall thickness to lumen. A uniformly applied external pressure to an extremity during diastole would therefore be expected to collapse the larger, proximal vessels first, thereby impeding return of blood to the central aorta.

The sequenced pulsator consists of arm and leg sections which are divided into multiple zones, each of which may be individually and separately activated to externally compress the enclosed body tissue. Activation is accomplished by inflating a chamber in each zone with compressed air. Flexible hoses connect the pressure enclosures for the arms and legs to the pressure and timing controller. The electrocardiographic signal from the patient directs the sequenced inflation of the zones through a series of solenoid valves. At the onset of the QRS complex, all pressure is simultaneously evacuated from the extremity cuffs. With such a mode the heart will never pump against a pressure wave produced by the assist device. The onset of cuff inflation can be set manually according to the length of cardiac systole. At the onset of cardiac diastole the sequenced pressure inflation is begun.

Inflating the cuffs at the beginning of diastole returns blood to the central circulation with a consequent rise in central aortic pressure. When the ventricle contracts there is diminished resistance in the periphery due to the previous emptying of arterial blood into the central circulation during the previous diastole. Sequenced pulsation has a milking effect upon the arterial and venous beds as pressure is applied sequentially from more distal to proximal sites. Although the sequenced pulsator has not yet been utilized in the therapy of patients in cardiogenic shock, the preliminary laboratory results indicate that external sequenced pulsation can augment cardiac output and aortic diastolic pressure.

Circulatory assist devices have the combined aim of decreasing left ventricular work and also of increasing coronary bloodflow. It is hoped that by so doing a severely damaged left ventricle may be able to compensate and take over from the support device. Since cardiogenic shock is likely to be self-perpetuating once prolonged hypoperfusion of vital organs occurs, earlier application of assist devices may help certain patients in cardiogenic shock. It must be recognized, however, that even with the early application of an assist device, ischemic areas of myocardium may progress to the stage of necrosis. Acute revascularization of the myocardium with a saphenous vein bypass graft may be helpful and necessary in selected cases. The role of the circulatory assist device in these instances will be to stabilize the patient's condition while diagnostic studies such as selective coronary arteriography are performed. The success of this approach will have to be assessed as experience with saphenous vein bypass grafting increases and the long range prognosis of the grafts becomes clearer.